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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Gregory P. La Pointe
BACHMAN & LaPOINTE, P.C.
Suite 1201
900 Chapel Street
New Haven, CT 06510-2802

EXAMINER
HUYNH, PHUONG N

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1644	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/867,159	LORIA ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *5-9 and 19-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 10-18 and 26-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-32 are pending.

2. Applicant's election with traverse of Group I, Claims 1-18 and 26-32 (now claims 1-4, 10-18 and 26-32) drawn to an anti-allergic pharmaceutical composition comprising an active agent that read on the species of a specific inhibitor of histamine synthesis, filed 2/7/03, is acknowledged. The traversal is on the grounds that the inventions of Groups I-IV are unrelated, yet each of the groups contains claims 26-32. This is not found persuasive because of the reasons set forth in the restriction mailed 12/31/02. The histamine synthesis inhibitor and nucleotide primers in various pharmaceutical compositions differ with respect to their biochemical structures and mode of actions. Further, Groups I-IV are drawn to different Class and subclass. A search of Group I will not encompass the other groups. A prior art search also requires a literature search. It is a burden to search more than one invention. Therefore, the requirement of Group I (now claims 1-4, 10-18 and 26-32) and Groups II-IV is still deemed proper and is therefore made FINAL.

3. Claims 5-9 and 19-25 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-4, 10-18 and 26-32 drawn to an anti-allergic pharmaceutical composition comprising an active agent that read on the species of a specific inhibitor of histamine synthesis are being acted upon in this Office Action.

5. Claims 26-32 are objected to because of nucleotide primers and RNA sequence, which are drawn to non-election inventions.

6. Claim 1 is objected to because the article "An" before "anti-allergic pharmaceutical composition" is required.

7. Claims 2-3 are objected to because the article "The" before "anti-allergic pharmaceutical composition" is required.

8. Claim 4 is objected to because the article "A" before "pharmaceutical composition" is required.

9. Claims 10-18 and 26-32 are objected to because the article "The" before "pharmaceutical composition" is required.

10. Applicant should amend the first line of the specification to reflect the relationship between the instant application and foreign applications 01/05929 filed 5/3/01 and 01/04370 filed 3/30/01 as stated on the oath.

11. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

12. A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) is required. The substitute specification filed must be accompanied by a statement that it contains no new matter.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-4, 10-18 and 26-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an anti-allergic pharmaceutical composition comprising at least two active agents selected from the group consisting of (i) dust mite allergen peptides is selected from the group consisting of SEQ ID NO: 3-5, (ii) one antihistamine compound such as the ones recited in claim 10, (iii) one inhibitor of histamine synthesis wherein the inhibitor of histamine synthesis is tritoqualine which is also an inhibitor of histidine decarboxylase for treating allergic hypersensitivity by reduction of allergic reaction both on the upstream phase of IgE synthesis and reduction on the downstream phase of histamine synthesis and release; (2) the said anti-allergic pharmaceutical composition comprising (i) at least one allergen peptides selected from D Pteronyssinus and D. Farinae, (ii) and at least one antihistamine compound such as the one recited in claim 10, and a pharmaceutically acceptable vehicle; (3) The said pharmaceutical composition wherein the allergen is a major antigen of acarids or a mixture of allergen selected from the group consisting of SEQ ID NO: 3-4; (4) the said pharmaceutical composition wherein the allergen is of the order of 1 to 1500 μg or from 10 to 150 μg; (5) the said pharmaceutical composition wherein the antihistamine compound is of the order of 1 to 2000 mg or from 5 to 200 mg; (6) the said pharmaceutical composition further comprises an inhibitor of histamine synthesis, and (7) the said pharmaceutical composition further comprises an inhibitor of histamine synthesis wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase tritoqualine between 10 and 300 mg and wherein the antihistamine compound is from 5 to 200 mg for treating allergic hypersensitivity by reduction of allergic reaction both on the upstream phase of IgE synthesis and reduction on the downstream phase of histamine synthesis and release in children, infants and adults, **does not** reasonably provide enablement for (1) *any* anti-allergic pharmaceutical composition as set forth in claims 1-3 or (2) *any* pharmaceutical composition as set forth in claims 4, 10-18, 26-32 for "preventing" any

allergic hypersensitive reactions such as asthma, rhinitis, atopic or allergic eczema or allergic symptoms in children, infants and adults. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two allergens from dust mite of *D. Pteronyssinus* (DP) comprising SEQ ID NO: 1 and *D. Farinae* (DF) comprising SEQ ID NO: 2 (page 5). The specification further discloses three allergen peptides wherein the peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3-5 that are derived from the cysteine protease of dust mite D. Pteronyssinus (DP) of SEQ ID NO: 1 and D. Farinae (DF) (See page 6). The specification discloses a pharmaceutical composition comprising (i) allergen peptide mentioned above, (ii) an antihistamine compound such as the ones recited in claim 10 and (iii) tritoqualine which is a histamine synthesis inhibitor and a histidine decarboxylase inhibitor and (iv) a pharmaceutical acceptable vehicle (page 10-11) for induction of tolerance to dust mite and to block the histamine synthesis, which is the terminal phase of allergy.

The specification does not teach how to make and use *any* anti-allergic pharmaceutical composition other than the specific pharmaceutical mentioned above because there is insufficient guidance as to the structure of *any* allergen, *any* major antigens among the undisclosed antigens of acarids without the specific amino acid sequence (SEQ ID NO). Further, there is insufficient guidance as to the structure of any antihistamine, any inhibitor of histamine, and any inhibitor of histidine decarboxylase, much less in vivo working example using any pharmaceutical composition.

Stryer *et al* teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Fasler *et al* teach that peptides derived from house dust mite Der p1 are modified by even a single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular).

With regard to "antihistamine compound, inhibitor of synthesis or inhibitor of histidine decarboxylase", the '345 patent teaches drugs known to block the effects of chemical mediators of the allergic reactions such as antihistamines, are used to control the severity of the allergic symptoms and antihistamines **do not prevent** the allergic reactions or **prevent allergic response** to subsequent allergen exposure (See column 1 line 65 bridging column 2 lines 1-4, in particular). Even if the anti-allergic pharmaceutical composition is limited to the specific allergen and the specific anti-histamine compound, the term "preventing" is problematic because the term "prevent" as define by the Webster's II New Riverside University Dictionary as "to keep from happening or to anticipate or counter in advance". The specification fails to provide guidance as how to select or identify an individual before allergy symptoms begin, how to predict who would or would not get allergy, let alone preventing allergy from happening. Given the indefinite number of undisclosed allergen, major antigen of any allergen, major antigen of acarids, antihistamine compound, inhibitor of synthesis or inhibitor of histidine decarboxylase, a person of skill in the art would not know which undisclosed allergen such as the major antigens or major antigens of acarids is essential and which undisclosed antihistamine, inhibitor of histamine, inhibitor of histidine decarboxylase could treat, let alone to "prevent" allergic hypersensitive reactions such as asthma, allergic rhinitis, atopic and allergic eczema, and allergic symptoms. For these reasons, it would require undue experimentation of one skilled in the art to practice the

claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

15. Claims 1-4, 10-18 and 26-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* anti-allergic pharmaceutical composition as set forth in claims 1-3 or (2) *any* pharmaceutical composition as set forth in claims 4, 10-18, 26-32 for "preventing" any allergic hypersensitive reactions such as asthma, rhinitis, atopic or allergic eczema or allergic symptoms in children, infants and adults.

The specification discloses only two allergens from dust mite of *D. Pteronyssinus* (DP) comprising SEQ ID NO: 1 and *D. Farinae* (DF) comprising SEQ ID NO: 2 (page 5). The specification further discloses three allergen peptides wherein the peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NOS: 3-5 that are derived from the cysteine protease of dust mite D. Pteronyssinus (DP) of SEQ ID NO: 1 and D. Farinae (DF) (See page 6). The specification discloses a pharmaceutical composition comprising (i) allergen peptide mentioned above, (ii) an antihistamine compound such as the ones recited in claim 10 and (iii) tritoqualine which is a histamine synthesis inhibitor and a histidine decarboxylase inhibitor and (iv) a pharmaceutical acceptable vehicle (page 10-11) for induction of tolerance to dust mite and to block the histamine synthesis, which is the terminal phase of allergy.

With the exception of the specific peptide allergen and the specific histamine synthesis inhibitor mentioned above for an anti-allergic pharmaceutical composition, there is inadequate written description about the structure associated with function of *any* anti-allergic pharmaceutical composition containing (1) *any* active agent such as *any* allergen, any major

antigens or mixture of any major antigens of acarids, (2) "antihistamine compound", any (3) "inhibitor of histamine synthesis", (4) that enabling the release of any "peptides" and "other chemical substances" in independent manner at galenic level, (5) *any* allergen or antigens or mixture of any major antigens of acarids to induce any immune reaction, much less blocking any allergy because of the following reasons. The term "allergen" without the amino acid sequence such as SEQ ID NO has no structure, much less function. Likewise, the terms "antihistamine compound" and "inhibitor of histamine synthesis" without the chemical name have no structure, let alone having a specific function, in turn would be useful for an anti-allergic pharmaceutical composition. Other than the specific allergen peptides, and the specific inhibitor of histamine synthesis, there is inadequate written description about the structure associated with function of *any* active agent such as (1) *any* allergen, *any* major antigens, *any* mixture of any major antigens of acarids, (2) *any* "antihistamine compound", (3) *any* "inhibitor of histamine synthesis", any "inhibitor of histidine decarboxylase" for treating any allergy, much less to "prevent" any allergy. Since the allergen, antihistamine compound, inhibitor of histidine synthesis and inhibitor of histidine decarboxylase are not adequately described, it follows any pharmaceutical composition containing any quantity of allergen such as the ones recited in claim 14, any quantity of antihistamine compound such as the ones recite in claims 15 and any quantity of inhibitor of histamine synthesis such as the ones recited in claims 17-18 are not adequately described. Since the pharmaceutical composition mentioned above is not adequately described, it follows that any pharmaceutical composition that permits the TH2/TH1 switch and reduction of allergic reaction both on the upstream phase such as IgE synthesis, and on the down stream phase such as synthesis and release of histamine is not adequately described. It also follows that any pharmaceutical composition that is released in the form of a transcutaneous patch or in the form of eye lotion, nasal spray or galenical form is not adequately described.

Further, the specification discloses only one histidine decarboxylase which is tritoqualine, and three specific allergen peptides of SEQ ID NO: 3-5 which are the major antigens from only dust mite of *D. Pteronyssinus* (DP) comprising SEQ ID NO: 1 and *D. Farinae* (DF) comprising SEQ ID NO: 2. Given the lack of a written description of *any* additional representative species of allergen, major antigen of any allergen, major antigen of acarids, inhibitor of histamine synthesis, inhibitor of histidine decarboxylase as encompassed by the claims for an anti-allergic composition to treat or "prevent" allergic hypersensitive reactions such as asthma, allergic rhinitis, atopic and allergic eczema in children, infants, and adults, one of skill in the art would

reasonably conclude that the disclosure fails to provide a representative number of species of allergen, inhibitor of histamine synthesis and inhibitor of histidine decarboxylase to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

17. Claims 3-4, 10-18, and 26-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "characterized in that" in claims 3-4, 10-18, 26-32 is ambiguous and indefinite because it is not clear which characteristics of the claimed composition that Applicants intend to claim. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The recitation of "enabling release of the peptides and other chemical substances in independent manner at galenic level" in claim 3 is ambiguous and indefinite because the specification does not define what is meant by galenic level and it is also not clear which chemical substances and peptides are being release. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The recitation of "said compounds" in claim 11 line 4 is ambiguous because it is not clear the compounds are referring to that anti-histamine compound at line 3 and/or inhibitor of histamine synthesis.

The phrase "such as" in claim 18 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Further, the specification discloses only tritoqualine as the histidine decarboxylase inhibitor.

The recitation of "it is released in mucosal, eye lotion, nasal spray or bronchial form" in claim 28 is ambiguous because the pharmaceutical preparation can be administered in the form of eye lotion, or nasal spray to be released to the mucosal surface.

The recitation of "a galenical form with programmed mucosal or sublingual and secondarily per os disintegration" in claim 29 is ambiguous because it is not clear what is meant by galenical form or secondarily per os disintegration, let alone programmed mucosal or sublingual. The specification does not define the term "galenical form" and "secondarily per os disintegration".

The recitation of "inhibitor of histamine synthesis of between 1 and 2000 mg" in claim 17 has no support in the specification as filed. The specification on page 12 at line 6 discloses that the inhibitor of histidine decarboxylase is between 10 to 300 mg. The specification further discloses on page 11 at line 27 that the antihistamine compound is of the order of 1 to 2000 mg. Appropriate correction is required.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(e) the invention was described in a **patent** granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an **international application** by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

19. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

20. Claims 1-4, 14, and 26-32 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 6,455,686 (Sept 2002, PTO 892).

The '686 patent teaches an anti-allergic pharmaceutical composition comprising an allergen such as high molecular weight Dermatophagoides farinae proteins from mite in conjunction with other compound such as anti-histamines (column 42, lines 40-59, in particular) associated with a pharmaceutical acceptable vehicle such as phosphate buffered saline (PBS, see column 44, line 63 bridging column 45, line 1, in particular) in a controlled released formulation such as liposome, transdermal delivery systems, or osmotic pumps (See column 41, lines 20-33, in particular). The reference whole dust mite allergen from Dermatophagoides farinae inherently contains the major antigens of acrid which is capable of induce an immune reaction such as immediate hypersensitivity response (See column 51, Table 2, lines 13-15, in particular). The reference pharmaceutical composition contains from about 0.5 ng to about 1 g per kg body weight (See column 42, lines 26-28, in particular). The '686 patent further teaches a composition comprising anti-inflammatory agent or compound such as peptides from IgE or IgE specific Fc receptors or antibodies capable of binding to IgE and blocks IgE binding to Fc receptors that drive immunoglobulin heavy class switching from IgE to IgG which inherently switch from Th2 to Th1 that reduce IgE synthesis in the upstream phase while the reference anti-histamine inhibits the histamine release in the down stream phase (See column 42, lines 45-49, in particular). The reference pharmaceutical composition is administered in form of subcutaneous, intradermal, intravenous, nasal, oral, transdermal and intramuscular routes (See column 42, lines 35-39, in particular). The reference pharmaceutical composition is useful to treat allergic hypersensitivity reactions to dust mite such as allergic asthma, allergic rhinitis, atopic and allergic eczema or to desensitize humans who are allergic to dust mite (See column 36, lines 31-36, column 42, lines 60-63, in particular). The reference pharmaceutical composition contains a quantity of 1×10^{-8} microgram to about 100 μg or from about $1x\ 10^{-7}$ μg to about 10 μg (See column 27, lines 31-34, in particular). Claim 14 is included in this rejection because the claimed limitations of 1 to 1500 μg or from 10 to 150 μg include the reference quantity of allergy. Thus, the reference teachings anticipate the claimed invention.

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 1-4, and 10-13, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 6,455,686 (Sept 2002, PTO 892) in view of US Pat No 4,302,458 (Nov 1981, PTO 892) and US Pat No 6,258,816 (July 2001, PTO 892) or US Pat No. 5,827,852 (Oct 1998, PTO 892) or US Pat No 6,319,513 (Nov 2001, PTO 892).

The teachings of '686 patent have been discussed supra.

The claimed invention as recited in claim 10 differs from the teachings of the reference only that the pharmaceutical composition wherein the antihistamine compound is brompheniramine, cetirizine, fexofenadine, cyproheptadine, dexchlorpheniramine, hydroxyzine, ketotifen, loratidine, mequitazine, oxotomide, mizolastine, ebastine, astemizole, carbinoxamide, alimemazine, buclizine, cyclizine, hydrochlorate, and doxylamine.

The claimed invention as recited in claim 11 differs from the teachings of the reference only that the pharmaceutical composition contains at least one antihistamine compound and at least one inhibitor of histamine synthesis and a pharmaceutical acceptable vehicle.

The claimed invention as recited in claim 12 differs from the teachings of the reference only that the pharmaceutical composition wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase.

The claimed invention as recited in claim 13 differs from the teachings of the reference only that the pharmaceutical composition wherein the inhibitor of histamine synthesis is an inhibitor of histidine decarboxylase is tritoqualine.

The claimed invention as recited in claim 15 differs from the teachings of the reference only that the pharmaceutical composition wherein the quantity of antihistamine compound is of the order of 1 to 2000 mg or from 5 to 200 mg.

The claimed invention as recited in claim 16 differs from the teachings of the reference only that the pharmaceutical composition contains an inhibitor of histamine synthesis.

The claimed invention as recited in claim 17 differs from the teachings of the reference only that the pharmaceutical composition contains a quantity of inhibitor of histamine synthesis of between 1 and 2000 mg.

The claimed invention as recited in claim 18 differs from the teachings of the reference only that the pharmaceutical composition contains an antihistamine from 5 to 200 mg and from 10 to 300 mg of an inhibitor of histidine decarboxylase tritoqualine.

The '458 patent teaches a pharmaceutical composition comprising tritoqualine which has been known for its anti-allergy properties and its derivative such as 458 L (See column 1, lines 11-13, in particular). The reference tritoqualine and 458 L are histamine decarboxylase inhibitor (See column 5, lines 3-10, Table, in particular) and are useful in treatment of allergy conditions such as pollinoses, uriticaria, eczema (See column 5, lines 30-33, claims 7-9, in particular). The '458 patent further teaches that the reference pharmaceutical composition can be administered orally, rectally, in a daily dosage of 20 to 500 mg and in the forms of tablets, pills, or suppositiories wherein the reference dosage is within the claimed dosage of between 1 and 2000 mg, the claimed dosage of from 5 to 200 mg (See column 5, lines 34-37, in particular).

The '816 patent teaches anti-allergy anti-inflammatory composition comprising an antihistamine such as cetrizine at a dose of 1.16mg/kg and an anti-leukotriene such as Nimesulide for asthma (See claims 1-6 of '816 patent, in particular). The '816 patent teaches various Histamine receptor antagonist such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine for treatment of allergic rhinitis as they are long acting and are free from sedative and anticholinergic effects (See column 4, lines 43-47, in particular). The '816 patent further teaches that cetirizine is very effective in inhibiting the cutaneous early and late phase response by inhibiting PAF and eosinophil recruitment in skin (See column 5, line 3-5, in particular).

The '852 patent teaches various pharmaceutical composition comprising various sedating antihistamine such as chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine for treating allergy (See summary of Invention, column 6, lines 5-20, claims 1, and 6-12 of '852 patent, in particular).

The '513 patent teaches various pharmaceutical composition comprising various sedating antihistamine and non-sedating antihistamines such as dexchlorpheniramine, cyproheptadine, fexofeadine, loratidine, ebastine, astemizole, hydrozyzine (See column 10, lines 55 bridging column 11, lines 1-2, in particular). The '513 patent teaches that the reference composition is administered usually from 0.5 mg/kg to about 500 mg/kg per day, which is equivalent to 25 mg to 50 mg for an average person of 50 kg. The '513 patent teaches that the reference composition is administered from about 1 mg/kg to about 300 mg/kg per day, which is equivalent to 50 mg to 15000 mg or preferably from about 5 mg/kg per day to about 200 mg/kg per day, which is equivalent to 250 to 10,000 mg per day (See column 16, lines 23-31, in particular). Claims 15 and 18 are included in this rejection because the claimed limitation of 1 to 2000 mg or from 5 to 200 mg is within the purview of the one ordinary skill in the art at the time the invention was made as taught by the'513 patent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antihistamine as taught by the '686 patent for the histamine synthesis inhibitor which is also a histidine decarboxylase inhibitor such as tritoqualine as taught by the '458 patent or to combine the various antihistamine such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine taught by the '816 patent, or the chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine taught by the '852 patent and '513 patent in an anti-allergic pharmaceutical composition comprising any allergen and any antihistamine as taught by the '686 patent and the '458 patent or the '852 patent or the '513 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '458 patent teaches that decarboxylase inhibitor such as tritoqualine and 458 L are histamine decarboxylase inhibitor (See column 5, lines 3-10, Table, in particular); they are useful in

treatment of allergy conditions such as pollinoses, uriticaria, eczema (See column 5, lines 30-33, claims 7-9, in particular). The '816 patent teaches that histamine receptor antagonist such as cetirizine, fexofenadine, acrivastine, asthmizole, and loratidine for treatment of allergic rhinitis as they are long acting and are free from sedative and anticholinergic effects (See column 4, lines 43-47, in particular) and that cetirizine is very effective in inhibiting the cutaneous early and late phase response by inhibiting PAF and eosinophil recruitment in skin (See column 5, line 3-5, in particular). The '852 patent teaches that various sedating antihistamine such as chlorpheniramine, brompheniramine dexchlorpheiramine, cyproheptadine, hydroxyzine, and various non-sedating antihistamine such as ketotifen, loratidine, oxatomide, astemizole, and ebastine are useful for treating allergy (See summary of Invention, column 6, lines 5-20, claims 1, and 6-12 of '852 patent, in particular). The '686 patent teaches an anti-allergic pharmaceutical composition comprising any allergen in conjunction with anti-histamines (column 42, lines 40-59, in particular) associated with a pharmaceutical acceptable vehicle such as phosphate buffered saline (PBS, see column 44, line 63 bridging column 45, line 1, in particular) is useful to desensitize humans who are allergic to dust mite (See column 36, lines 31-36, column 42, lines 60-63, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ... [T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

26. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 24, 2003

Phillip Gambel
PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
3/24/03